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(58) Field of Search

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(54) Abstract Title

Injectable halogenated anesthetic formulation in emulsion form

(57) An injectable anaesthetic formulation comprises a halogenated anaesthetic compound, such as desflurane, isoflurane, enflurane, halothane or sevoflurane, but preferably isoflurane, and at least one emulsifier, preferably soybean oil. Although not essential, it is preferred to also include lecithin (an emulsifier also) and a co-emulsifier such as a polyoxyethylene-polyoxypropylene block copolymer, for example, poloxamer 188. The composition may further contain water, a pH adjustment agent, such as sodium hydroxide, and/or glycerol. It is preferred that the halogenated anaesthetic has a boiling point between 20° and 60°C. An example of such a formulation comprises isoflurane (10 ml); soybean oil (10 ml); glycerol (2.5 g), lecithin (1.8 g) and water (q.s.). The proportion of anaesthetic to emulsifier should be, at a minimum, 1 part emulsifier to 3 parts anaesthetic in order to ensure the formation of a stable emulsion. The total amount of dispersed non-aqueous phase (anaesthetic plus emulsifier(s)) should be less than or equal to about 32% v/v in order to provide a solution of suitable viscosity for administration by injection.

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INJECTABLE ANESTHETIC FORMULATION

Technical Field of the Invention

The field of the present invention is anesthetics. More particularly, this
5 invention pertains to an injectable anesthetic formulation. - -

Background of the Invention

Inhalation anesthetics such as isoflurane and sevoflurane are commonly
used for anesthetizing patients for medical procedures. Although inhalation
10 anesthetics are suitable for many medical procedures, they do have certain
disadvantages. For example, induction of anesthesia by inhalation can be
relatively slow in some patients. Further, the use of inhalation anesthetics
requires the patient to breathe the anesthetic using a gas containment mask.
The wearing of such a containment mask can be upsetting for some patients,
15 particularly children. For these and other reasons, rapid anesthetic induction is
commonly performed by intravenous injection using relatively short acting
agents such as propofol. Inhalation anesthetics are then used to maintain the
anesthetized condition.

Inhalation anesthetics such as isoflurane and sevoflurane generally have
20 been deemed unsuitable for parenteral administration due to their low aqueous
solubility, thereby making it difficult to formulate them for intravenous
administration, i.e., their low solubility results in unacceptably large dose
volumes.

The need for a suitable formulation for injection has been recognized in
25 the art. For example, U.S. Patent No. 5,637,625 discloses a phospholipid-coated,
microdroplet propofol formulation. The disclosed formulation is devoid of fats
and triglycerides so that the formulation provides sedation without fat overload.
In addition, the formulation is free of nutrients capable of supporting bacterial
growth, thereby providing the formulations with an increased shelf life. In
30 addition, the use of lecithin-coated microdroplets of methoxyflurane was

described in "Pharmacokinetics of Methoxyflurane After its Intra-dermal Injection as Lecithin-coated Microdroplets," published in J. Controlled Release (1989), 9(1), 1 - 12. However, neither of these disclosures suggests the possibility of using an emulsion formulation of an inhalation anesthetic.

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Summary of the Invention

The present invention is directed to an injectable anesthetic formulation. In a first embodiment of the present invention, the formulation contains a halogenated anesthetic in an amount not greater than approximately 24% v/v of the formulation and an emulsification adjuvant in an amount from approximately 8% to approximately 32% v/v of the formulation. The formulation further contains lecithin in an amount from approximately 1.2% to approximately 2.4% w/v of the formulation and a co-emulsifier in an amount not greater than approximately 1% w/v of the formulation.

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Detailed Description of the Invention

Although the present invention has been described herein in connection with certain exemplary and preferred embodiments, it will be appreciated by one of ordinary skill that various modifications can be made to the invention without departing from the scope of the invention, such scope being defined by the appended claims.

The anesthetic formulations of the present invention have use in inducing maintaining anesthesia in humans and animals. The formulations include a halogenated volatile anesthetic having a boiling point between approximately 20° and approximately 60° C. Such halogenated volatile anesthetics include, but are not necessarily limited to, desflurane, isoflurane, enflurane, halothane, and sevoflurane. Each of these anesthetics is well-known in the art. Although the examples set forth herein disclose formulations containing isoflurane, it is to be understood that any halogenated anesthetic having the desired boiling point can be used in the formulations of the present invention.

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The formulations of the present invention further include an emulsification adjuvant such as soybean oil. Those of ordinary skill in the art will appreciate that other emulsification adjuvants having the characteristics of soybean oil can be used without departing from the spirit and scope of the present invention.

It has been found that a minimum ratio of 1 part emulsification adjuvant to 3 parts anesthetic is required in order to provide a stable emulsion. Further, it has been found preferable to provide an anesthetic formulation in which the total volume of dispersed phase, i.e., anesthetic and emulsification adjuvant, in the anesthetic formulation is below approximately 32% v/v in order to ensure that the viscosity of the resulting anesthetic formulation is acceptable for injection. In a preferred embodiment of the anesthetic formulation of the present invention, the halogenated anesthetic is present in an amount not greater than approximately 24% v/v while the emulsification adjuvant is present in an amount between approximately 8% and approximately 32% v/v.

The anesthetic formulation of the present invention further includes an emulsifier such as lecithin. Those of ordinary skill in the art will appreciate that other emulsifiers having the characteristics of lecithin can be used without departing from the spirit and scope of the present invention. The emulsifier is preferably present in an amount between approximately 0.6% and approximately 2.4% w/v. It has been found that emulsifier levels between approximately 1.2% and approximately 2.4% w/v are more preferable, and that emulsifier levels between approximately 1.8% and approximately 2.4% are most preferable in connection with the anesthetic formulation of the present invention.

The anesthetic formulation of the present invention further includes a co-emulsifier. An example of a co-emulsifier useful in connection with the anesthetic formulation of the present invention is a polyoxypropylene/polyoxyethylene block copolymer having a formula $\text{HO}(\text{C}_2\text{H}_4\text{O})_a(\text{C}_2\text{H}_6\text{O})_b\text{H}$ where a is an integer such that a molecular weight represented by a polyoxypropylene portion of the copolymer is between

approximately 900 to 15000, and b is an integer such that a molecular weight represented by a polyoxyethylene portion of the copolymer constitutes between approximately 5% and 90% of the copolymer. Those of ordinary skill in the art will appreciate that other co-emulsifiers having the characteristics of a polyoxypropylene/polyoxyethylene block copolymer can be used without departing from the spirit and scope of the present invention. In one embodiment of the present invention, poloxamer 188 is used as a co-emulsifier. The co-emulsifier is preferably present in an amount not greater than approximately 1% w/v, as explained in greater detail below, and more preferably in an amount not greater than approximately 0.96%.

It has been discovered that at a total emulsifier level (i.e., emulsifier content plus co-emulsifier content) of 1.8% w/v, a ratio of 8 parts of lecithin to 2 parts of poloxamer 188 provided desirable results in a 20% v/v isoflurane formulation due to an apparent reduction in droplet size and an increased resistance to creaming. Creaming is a form of emulsion instability well known in the art. However, it has been discovered that no stability benefits are obtained by the inclusion of poloxamer 188 in a 10% v/v isoflurane formulation. Accordingly, certain formulations in accordance with the present invention need not include a co-emulsifier such as poloxamer 188. Accordingly, as used herein, the term "in an amount not greater than" is intended to include the complete absence of a co-emulsifier from the anesthetic formulation of the present invention.

The anesthetic formulation of the present invention may further include a tonicifier such as glycerol. The tonicifier is used to adjust the tonicity of the anesthetic formulation to the tonicity of the patient's blood plasma. In a preferred embodiment of the anesthetic formulation of the present invention, the tonicifier is present in an amount between approximately 1% and approximately 4% of the formulation.

The anesthetic formulation of the present invention may also include a pH adjustor in an amount sufficient to adjust the pH of the formulation to between

approximately 6 and approximately 8, thereby making it suitable for injection and also for optimizing the stability of the emulsifier. A variety of known pH adjusters such as sodium hydroxide can be used in connection with the formulation of the present invention.

5 The preferred anesthetic formulation of the present invention further includes a vehicle for injection in a quantity sufficient for injection of the anesthetic formulation. Water can be used as the vehicle for injection.

10 The following examples are provided for the purpose of providing a further understanding of the anesthetic formulations of the present invention and are not intended to be limiting of the invention claimed in the appended claims.

Example 1:

A 10% v/v formulation of isoflurane was prepared. Each 100 ml of the resulting anesthetic formulation contained:

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isoflurane	10 ml
soybean oil	10 ml
glycerol	2.5 g
lecithin	1.8 g
distilled water	q.s.

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The soybean oil used in this example was winterized.

Example 2:

A 20% v/v formulation of isoflurane was prepared. Each 100 ml of the resulting anesthetic formulation contained:

5	isoflurane	20 ml
	soybean oil	10 ml
	glycerol	2.5 g
	lecithin	1.6 mg
	poloxamer 188	0.18 g
10	distilled water	q.s.

The soybean oil used in this example also was winterized. A pH adjustor (0.1 M sodium hydroxide) was added to adjust the pH of the resulting anesthetic formulation to between approximately 8 and approximately 9 prior to autoclaving of the resulting formulation.

Anesthetic formulations prepared in accordance with the present invention are suitable for terminal sterilization by autoclaving, e.g., heating to a temperature of approximately 121° C for approximately 15 minutes. This characteristic of the anesthetic formulations of the present inventions obviates the need for sterile processing.

Although the present invention has been described herein in conjunction with certain preferred embodiments and examples, it will be appreciated that certain modifications to the anesthetic formulation of the present invention can be made without departing from the intended spirit and scope of the present invention which is defined by the appended claims.

WHAT IS CLAIMED IS:

1. An injectable anesthetic formulation comprising:
a halogenated volatile anesthetic in an amount not greater than
approximately 24% v/v of said formulation;
an emulsification adjuvant in an amount from approximately 8% to
5 approximately 32% v/v of said formulation;
lecithin in an amount from approximately 1.2% to approximately
2.4% w/v of said formulation; and
a co-emulsifier in an amount not greater than approximately 1%
w/v of said formulation.
2. An injectable anesthetic formulation in accordance with
Claim 1, wherein said halogenated anesthetic is selected from a group consisting
of desflurane, isoflurane, enflurane, halothane, and sevoflurane.
3. An injectable anesthetic formulation in accordance with
Claim 1, wherein said halogenated anesthetic is isoflurane.
4. An injectable anesthetic formulation in accordance with
Claim 1, wherein said co-emulsifier is a polyoxypropylene/polyoxyethylene block
copolymer.
5. An injectable anesthetic formulation in accordance with
Claim 4, wherein said co-emulsifier is poloxamer 188.
6. An injectable anesthetic formulation in accordance with
Claim 4, wherein said co-emulsifier has a formula:
$$\text{HO}(\text{C}_2\text{H}_4\text{O})_a(\text{C}_3\text{H}_6\text{O})_b(\text{C}_2\text{H}_4\text{O})_a\text{H}$$

wherein a is an integer such that molecular weight represented by a

5 polyoxypropylene portion of said copolymer is between approximately 900 to 15000, and b is an integer such that a molecular weight represented by a polyoxyethylene portion of said copolymer constitutes between approximately 5% and 90% of said copolymer.

7. An injectable anesthetic formulation in accordance with Claim 1, wherein said emulsification adjuvant is soybean oil.

8. An injectable anesthetic formulation in accordance with Claim 1, wherein said formulation further comprises glycerol in an amount of between approximately 1% to approximately 4% w/v of said formulation.

9. An injectable anesthetic formulation in accordance with Claim 1, wherein said formulation further comprises water.

10. An injectable anesthetic formulation in accordance with Claim 1, wherein said formulation further comprises a pH adjustor.

11. An injectable anesthetic formulation in accordance with Claim 10, wherein said pH adjustor is sodium hydroxide.

12. An injectable anesthetic formulation comprising:
a halogenated anesthetic in an amount not greater than approximately 24% v/v of said formulation;
an emulsification adjuvant in an amount from approximately 8% to
5 approximately 32% v/v of said formulation;
lecithin in an amount from approximately 1.2% to approximately 2.4% w/v of said formulation; and
a co-emulsifier in an amount not greater than approximately 1% w/v of said formulation;

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a quantity of glycerol; and
a quantity of a pH adjustor sufficient to adjust a pH of said
formulation to between approximately 6 and approximately 9.

13. An injectable anesthetic formulation in accordance with
Claim 12, wherein said halogenated anesthetic is selected from a group
consisting of isoflurane, enflurane, halothane, and sevoflurane.

14. An injectable anesthetic formulation in accordance with
Claim 12, wherein said halogenated anesthetic is isoflurane.

15. An injectable anesthetic formulation in accordance with
Claim 1, wherein said co-emulsifier is a polyoxypropylene/polyoxyethylene block
copolymer.

16. An injectable anesthetic formulation in accordance with
Claim 15, wherein said co-emulsifier is poloxamer 188.

17. An injectable anesthetic formulation in accordance with
Claim 15, wherein said co-emulsifier has a formula:



5 wherein a is an integer such that molecular weight represented by a
polyoxypropylene portion of said copolymer is between approximately 900 to
15000, and b is an integer such that a molecular weight represented by a
polyoxyethylene portion of said copolymer constitutes between approximately 5%
and 90% of said copolymer.

18. An injectable anesthetic formulation in accordance with
Claim 12, wherein said emulsification adjuvant is soybean oil.

19. An injectable anesthetic formulation in accordance with Claim 12, wherein glycerol is present in an amount of between approximately 1% to approximately 4% w/v of said formulation.

20. An injectable anesthetic formulation in accordance with Claim 1, wherein said formulation further comprises water in an amount sufficient for injection of said formulation

21. An injectable anesthetic formulation in accordance with Claim 12, wherein said pH adjustor is sodium hydroxide.

22. An injectable anesthetic formulation substantially as herein described.



Application No: GB 9912446.3
Claims searched: 1-22

Examiner: Dr Lawrence Cullen
Date of search: 10 September 1999

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.Q): A5B

Int Cl (Ed.6): A61K 9/107

Other: Online: CAS ONLINE, EPODOC, JAPIO, WPI

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
X	Anesth. Analg., vol 88, 1999. J. B. Musser et al., "The Anesthetic and Physiologic Effects....", pages 671-75, see especially columns 1 & 2, page 671; Second paragraph, first column, p 672.	1, 2, 7, 9
X	Anesthesiology, vol 68, no 5, November 1985. D. H. Haynes at al., "Ultra-long-duration Local Anaesthetic produced by....", pages 490-499, see section entitled <i>Microdroplet Preparation</i> , pages 490-91; Appendix A, pages 498-99	1, 9, 10
X	Shinshu Igaku Zasshi, vol 18, no 4, 1969. T Kamijama. "Intravenous halothane anesthesia", pages 104-(838) to 114- (848), see Chemical Abstracts No 74:110157 and Figure 1, page 113-(847).	1, 2, 7, 9
X	Anesth. Analg., vol 47, no 5, September-October 1968. H. F. Cascorbi et al., "Hazards of Methoxyflurane Emulsions in Man.", pages 557-559, see especially column 1, page 557; Table, p 558	1, 4, 5, 7, 9
X	Anesth. Analg., vol 41, no 3, May-June 1962. J. C. Krantz et al., "Anesthesia LXIV:...", see pages 257-262, see especially section entitled <i>The Anesthetic Emulsion</i> on pages 257-8	1, 4, 5, 7, 9

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.



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Category	Identity of document and relevant passage	Relevant to claims
A	N. F. Estrin et al. (eds), The CTFA Cosmetic Ingredient Dictionary, 3rd edition, 1982, The Cosmetic, Toiletry and Fragrance Association, Inc., see page 238, entry re. 'Poloxamer 188'.	-
A	RBI Catalogue, 1999, Sigma-Aldrich Chemical Co. Ltd, Gillingham, UK; page 180, see entry I-141	-

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.